Remarks

Claims 1, 2, 7-48, 51, 53, 54, 57-63, and 65-79 are pending in the application. Claims 25, 28, 34-36, and 41-44 have been withdrawn from consideration by the Examiner. Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-48, 51, 53, 54, 57-63, and 65-79 stand rejected. Claims 1, 2, 60, 61, 63, 65, 69, and 73 have been amended, and claims 49-59 and 62 have been canceled. Support for the amendments to claims 1, 2, 63, 65, 69, and 73 is found in the specification (page 3, lines 4-5; page 25, lines 10-13; and "Methods of Making Microparticles" beginning on page 25, line 9), in Figure 1, and in original claims 51, 53, 57, 59, and 62. Support for amendments to claims 60 and 61 is found in original claims 60, 61, and 62. Applicant respectfully requests reexamination and reconsideration of the case in light of the following remarks. Each of the rejections levied in the Office Action is addressed individually below.

I. **Rejection under 35 U.S.C. § 112, second paragraph, as being indefinite.** Claims 1, 2, 7-24, 26, 27, 29, 30-33, 37-40, 45-48, 51, 53, 54, 57-63, and 65-69 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner maintains that the percent ranges specified in claims 1, 2, 63, and 73 are indefinite. Applicant respectfully submits that the present Amendment renders this rejection moot.

In addition, the Examiner maintains that the language used in claims 1, 2, 63, 69, and 73 to describe the preparation of the microparticles is indefinite, because it is unclear if "spray drying, single and double emulsion solvent evaporation, solvent extraction, phase separation, and simple and complex coacervation" are method steps of one process used to produce the claimed microparticles, or if they are separate methods that each might produce the claimed microparticles. These are distinct methods that can each be used to produce microparticles of the claimed invention, and the claims have been amended to incorporate proper Markush language as requested by the Examiner. Applicant respectfully asserts that the indefinite language as cited by the Examiner was not previously used in claim 63, but was instead used and is currently amended in claim 65.

II. **Rejection under 35 U.S.C. § 102(b) or § 103, in view of Sutton *et al.*, U.S. Patent 6,204,054.** Claims 1, 2, 7-17, 20-24, 26, 27, 29-33, 37-38, 40, 45-47, 51, 53, 54, 57-62, 65-70, 73-74, and 77-79 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Sutton *et al.* (U.S. Patent 6,204,054), or under § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054). The Examiner states that Sutton *et al.*, teaches the making of a matrix or microparticle composed of at least three components selected from a lipid, a protein, a sugar, and a polymer. And, therefore, the Examiner concludes that Sutton *et al.*, anticipates or renders obvious the claimed invention in the present application. The Examiner's reading of Sutton is incorrect. Sutton does not anticipate or render obvious the claimed invention.

The claims of the present application recite microparticles with a lipid-protein-sugar matrix or a matrix with at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. The claimed microparticles include *at least three* components in the matrix of the microparticles. Sutton does not teach microparticles with three matrix components such as a lipid, a protein, and a sugar. Sutton teaches the use of transcytosis vehicles and enhancers to deliver physiologically-active agents. Transcytosis vehicles and enhancers, as Sutton recites, are proteins including albumin, anti-GP60 antibodies, GP60 peptide fragments, protein disulphide isomerase (PDI), and fragments thereof (column 2, lines 46-51). Starting at column 7, lines 56, Sutton describes mixing the transcytosis enhancer or vehicle with a variety of other materials. The listed materials include sugars, polymers, and emulsifiers. The long list of possible materials for including with the transcytosis vehicles and enhancers in a microparticle does not constitute teaching one of skill in the art how to make lipid-protein-sugar microparticles or other particles with at least three components selected from the group consisting of lipids, proteins, sugars, and synthetic polymers. Sutton does not teach microparticles containing at least three components in the matrix, Sutton does not specifically describe such microparticles, and Sutton did not manufacture such microparticles (see Examples; in fact, Sutton does not demonstrate the preparation of microparticles of any kind). In contrast, Applicant specifically teaches, prepares, and tests microparticles with at least three matrix components. Without a teaching of this aspect of the invention, Sutton cannot anticipate or

render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

The Examiner states that Sutton teaches the making of a matrix or microparticle composed of at least three matrix components including a lipid (column 8, line 6), protein (column 3, lines 34-44), and sugar (lactose, column 7, line 10). The Applicant respectfully asserts that the mention of lactose in Sutton cited by the Examiner does not disclose lactose as a matrix or microparticle component. In fact, nowhere in Sutton is lactose mentioned as a possible matrix component. Lactose was mentioned in column 7, line 10 as an example of a pharmaceutically acceptable carrier or excipient to be used in the administration of the particles. The particles to be administered are dissolved in a solution containing a carrier or excipient *after* the particle is formed; therefore, the carrier or excipient (*e.g.*, lactose) is *not* a component of the matrix or microparticle. That is, lactose was part of a pharmaceutical composition including Sutton's microparticles, but lactose was not part of the microparticles themselves as claimed in the present application. Without a teaching of lactose or another sugar, Sutton cannot anticipate or render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

Furthermore, Sutton does not teach the aspects of the claims recited in claims 38 (wherein the sugar is *lactose*) and 79 (matrix comprising dipalmitoylphosphatidylcholine (DPPC), *lactose*, and albumin). Since Sutton does not specifically teach microparticles containing lactose, Sutton cannot anticipate these claims. Applicant, therefore, respectfully requests that the rejection be removed.

Furthermore, solely to further prosecution, Applicant has amended independent claims 1, 2, 63, 65, 69, and 73 to recite specific ranges for each of the components, lipid, protein, and sugar (supported by original claims 51, 53, and 57). As amended, the matrix of the claimed particles contains 20-60% by weight lipid, 10-30% by weight protein, and 10-30% by weight sugar. Sutton teaches microparticles with "at least 50%, more preferably 70 or 80%, and most preferably 90%, by weight transcytosis enhancer" (column 9, lines 8-10). As noted above, transcytosis enhancers are proteins. Therefore, Sutton teaches particles of "at least 50%" protein

and does not teach microparticles containing 10-30% by weight protein. In fact, Sutton teaches away from the claimed particles. Applicant respectfully requests that the rejection be removed.

Additionally, Sutton teaches "hollow particles enclosing a space, which space is filled with gas or vapour but not with any solid materials" (column 8, lines 42-43). Sutton also specifically teaches that methods for making microparticles should be optimized to "ensure hollowness" (column 8, line 64). The claims of the present application recite solid microparticles in which the agent is "encapsulated in a lipid-protein-sugar matrix" (page 3, lines 4-5) implying that the agent can be either dispersed throughout the matrix and/or *contained within the polymeric shell.* Furthermore, a scanning electron micropgraph of a spray dried lipid-protein particle is shown in Figure 1 indicates that the particles are substantially solid and not hollow. Also, various methods of preparing inventive microparticles are described, including spray drying, single and double emulsion solvent evaporation, and solvent extraction (page 25, lines 10-13), which are methods that yield substantially solid particles. Therefore, Applicant submits that one of skill in the art reading the specification would understand that the particles of the present invention are substantially solid and are not hollow. Given that Sutton teaches hollow microparticles, Sutton does not anticipate the claimed invention. Applicant respectfully requests that the rejection be removed.

III. Rejection under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054) taken with Grinstaff *et al.* (U.S. Patent 5,639,473). Claims 1, 18, 19, 69, and 71-76 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sutton *et al.* (U.S. Patent 6,204,054) in view of Grinstaff *et al.* (U.S. Patent 5,639,473). The Examiner cites Grinstaff *et al.* for the teaching that it is well established in the art that DNA immunogenic compositions can be used in combination with a polymeric or particle based carrier for enhancing the controlled release and bioavailability of an expressed antigen *in vivo.*

Even if Grinstaff teaches the combination of DNA plus a polymeric or particle-based carrier, neither Sutton nor Grinstaff taken together or separately teaches particles with a lipid-protein-sugar matrix. Sutton and Grinstaff merely include exhaustive lists of many different excipients, polymers, emulsifiers, sugars, *etc.*, which might be included in the microparticles.

Such a teaching is not novelty destroying, and such a teaching does not render the claimed invention obvious. Although Sutton and Grinstaff list various agents that may be added to their protein particles (see Sutton, columns 7-8 and Grinstaff, column 12), neither reference describes or produces a particle with a matrix of lipid, protein, and sugar, or even a particle with three components in the matrix. Certainly, a laundry list of materials that might be included in a particle cannot suffice to be an enabling and patentability destroying reference with respect to the claimed invention which recites three components in the particles. In contrast to Sutton and Grinstaff, the inventors of the present application have successfully produced the microparticles with three components and successfully used the microparticles for drug delivery in a live mammalian model system.

Furthermore, Applicant has amended independent 1, 2, 63, 65, 69, and 73 to recite specific ranges for the lipid, protein, and sugar in the matrix. Sutton, as discussed above, does not teach the specified range of protein in the matrix (10-30% by weight), but instead teaches at least 50% by weight (column 9, lines 8-10). Grinstaff does not teach the ranges recited in the claims for the individual matrix components. The Examiner must point out an explicit teaching of all aspects of the claimed invention, including the specified ranges of each component, in order to establish a *prima facie* case of obviousness. Since the references, even when combined, do not teach all aspects of the invention, the Applicant respectfully requests that the rejection be removed.

In addition, Grinstaff discloses microparticles with a substantially cross-linked polymeric shell made of biocompatible material cross-linked by the presence of disulfide bonds (column 6, lines 13-14 and column 8, lines 8-10). In column 8, lines 34-53, Grinstaff describes the materials of the polymeric shell as bearing sulfhydryl groups, disulfide groups, or precursors of esters, amides, ethers, and the like that can be used in forming microparticles and used for cross-linking. These materials used in the particles undergo cross-linking during ultrasonic irradiation to create the particles described in Grinstaff.

The specification of Grinstaff focuses on the critical nature of cross-linking to the functionality of their microparticles. The specification describes several reasons that a cross-linked polymer shell is advantageous over non-cross-linked microparticles, such as better

protection against leakage of the encapsulated agent (column 20, lines 18-22) and less aggregation of microparticles (column 20, lines 22-25). If a material does not contain moieties that are suitable for cross-linking, that material cannot be used unless it is chemically modified to contain such moieties (column 8, lines 34-53). For example, if a protein without naturally-occurring cysteine residues is to be used in the matrix (*e.g.* myoglobin), this protein must be genetically engineered to contain "at least two cross-linkable cysteine reidues" in order to be a suitable component of the polymeric shell described by Grinstaff (column 20, lines 2-8). As another example, polyethylene glycol (PEG) can be an additional component of the matrix described in Grinstaff, but only if PEG is first chemically modified to contain sulfhydryl groups and then subjected to cross-linking during the formation of the polymeric shell (column 12, lines 60-63). Grinstaff teaches the critical nature of cross-linking to form microparticles and therefore teaches away from microparticles that have been formed without a cross-linking step and without components suitable for cross-linking.

In contrast, the microparticles of the claimed invention are prepared *without* a cross-linking step and therefore would *not* include a substantially cross-linked polymeric shell as described by Grinstaff. Support for amended claims 1, 2, 63, 65, 69, and 73 can be found in the subsection entitled "Methods of Making Microparticles" (beginning on page 25, line 9). This section describes the preparation of the inventive microparticles and does not describe any step which would achieve cross-linking of the matrix components. Specifically, there are no steps using heat, light, or ultrasound to effect cross-linking of the matrix components to form a substantially cross-linked polymeric shell. In the Examples, microparticles were prepared using the disclosed methods and were therefore prepared with no cross-linking step. In the absence of such a step , the matrix of the microparticles of the claimed invention does not include a cross-linked polymeric shell. Microparticles prepared with no cross-linking step and containing no cross-linking shell were shown to successfully and safely deliver a therapeutic agent in an animal model system, which is in contrast to the teachings of Grinstaff.

The polymeric shell of the microparticles described by Grinstaff can be further modified by lipids, proteins, or sugars, but such modifications must be covalently bound to the surface of the already-formed polymeric shell and are not themselves components of the matrix of the

polymeric shell (column 12, lines 12-31). In contrast, the lipids, proteins, and sugars of the microparticles of the claimed invention are themselves components of the microparticle matrix, and are not merely attached to the surface of the matrix as modifications.

The microparticles of the claimed invention as amended include a matrix comprising three components and do *not* include a substantially cross-linked polymeric shell. Additionally, the components used in the inventive particles do not need to contain sulfhydryl groups or other functional groups suitable for cross-linking. Applicant, therefore, respectfully requests that the rejection be removed.

In the Office Action dated January 11, 2005, claims including the limitation "lipid, protein, and sugar of the matrix are not part of a substantially cross-linked polymeric shell" were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claims were previously amended to remove any mention of the cross-linked shell but are now currently amended to include this limitation. Applicant asserts that a limitation in the claims stating "lipid, protein, and sugar in the matrix are not part of substantially cross-linked particles" does not constitute new matter. Applicant respectfully directs the Examiner to the case of *In re Johnson*, in which this issue was addressed. Johnson sought to limit his claims drawn to a genus of polymers by excluding two species, which had been the subject of a lost count in an interference. 558 F.2d 1008, 194 USPQ 187 (CCPA 1977). The Patent Office held that Johnson was not entitled to the original filing date of July 16, 1963 because the "presently claimed subject matter is not 'described' in the 1963 application as required by the first paragraph of 35 U.S.C. § 112." The Board of Appeals affirmed the Examiner's rejection. However, the CCPA in this case reversed the rejection under 35 U.S.C. § 112 and held:

> "The notion that one who fully discloses and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of § 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute."

Id. The court further held that the "appellants are merely excising the invention of another, to which they are not entitled, and are not creating an 'artificial subgenus' or claiming 'new matter.'" In light of the court's opinion, the limitation of "not part of substantially cross-linked particles" is present simply to exclude the invention of another and is not claiming new matter. Therefore, the Applicant respectfully requests that the rejection be removed because it does not constitute new matter.

Furthermore, there is no teaching or suggestion to combine Grinstaff and Sutton. In fact, the teachings of Grinstaff and Sutton are mutually exclusive. Grinstaff teaches methods for delivering physiologically-active agents, and such methods comprise "entrapping biologics in a polymeric shell" (column 6, lines 37-38), "wherein said biologic is substantially completely contained within a polymeric shell" (column 10, lines 9-10). Grinstaff teaches microparticles which deliver physiologically-active agents by *encapsulating the agents*, such as fluorophores (column 34, Example 5), pharmaceutically active agents (columns 36-37, Example 8) organofluorine-containing compounds (column 42, Example 16 and columns 48-49, Examples 33-37), water-soluble drugs (columns 44-45, Example 23), and proteins (column 45, Example 24) in a polymeric shell. As mentioned above, Sutton teaches *hollow* microparticles for the delivery of physiologically-active agents (column 8, lines 42-43, 55). Sutton and Grinstaff both teach microparticles that deliver physiologically-active agents, but the functional particles in these two references have a mutually exclusive physical characteristics: microparticles cannot simultaneously be hollow and encapsulate the agent to be delivered. Therefore, these references cannot be combined to establish a *prima facie* case of obviousness. Since the references cannot be properly combined to teach all aspects of the invention, the Applicant respectfully requests that the rejection be removed.

IV. Rejection under 35 U.S.C. § 103 as being unpatentable over Hanes *et al.* (U.S. Patent 5,855,913). Claims 1, 2, 7-24, 26, 27, 29-31, 33, 37-40, 45-48, 51, 53, 54, 57-63, 65-69, and 73-78 stand rejected under 35 U.S.C. § 103 as being unpatentable over Hanes *et al.* (U.S. Patent 5,855,913). The Examiner maintains that Hanes *et al.*, teaches "a polymeric microparticle of less

than 10 μm in diameter for use as a controlled release-encapsulated carrier of biologically active molecules such as DNA or DNA coding for a gene of interest, wherein the microparticles are composed of a combination of biocompatible materials selected from DPPC, copolymers, protein excipients (any known polymeric polypeptide or copolymers thereof) and a sugar (lactose). Applicant disagrees with the Examiner's assessment of Hanes *et al.*

Hanes discloses microparticles that have a mean diameter between 5 μm and 30 μm (column 3, line 67-column 4, line 2). In particular, Hanes teaches that particles larger than 5 μm deliver therapeutic, diagnostic, and pharmeceutical agents more effectively than smaller particles (column 8, lines 8-12). Hanes teaches that particles larger than 5 μm can more successfully avoid phagocytotic engulfment, due to size exclusion of phagocytes' cytosolic space (column 8, lines 29-34). Given that Hanes teaches that particles smaller than 5 μm deliver the agent less effectively than particles larger than 5 μm, the results of the experiments presented in the examples of the present application are surprising and unexpected. The lipid-protein-sugar particles that were described in the examples were all smaller than 5 μm (page 35, Table 1, and page 52, Table 2). Hanes would predict that particles of this size would be engulfed by phagocytes and, therefore, would not effectively deliver the agent. However, this is not the result of the experiments described in the current specification. Instead, the lipid-protein-sugar particles are stable within the animal, are able to effectively deliver the agent, and are able to elicit the desired pharmaceutical effect (pages 38-39, "*Effectiveness of sciatic nerve block*"). Hanes cannot render obvious the claimed microparticles that are smaller than 5 μm. Therefore, Applicant respectfully requests that the rejection be removed.

Hanes teaches particles incorporating a surfactant for drug delivery to the pulmonary system. Hanes states that the surfactant may be incorporated throughout the particle or may be coated on the particle's surface. The reference also lists many exemplary surfactants for use in the particles. The surfactant improves various surface properties of the particles including reducing particle-particle interactions. Hanes describes the particles as being formed from biocompatible polymers such as polyanhydrides, polycarbonates, polyalkenes, and other synthetic polymers; celluloses; polysaccharides; peptides; and proteins. Particles formed from only surfactant and the agent to be delivered are also described. Hanes does *not* teach or suggest

the particular combinations of materials recited in the claims (*e.g.*, lipid, protein, and sugar). Furthermore, Hanes does *not* teach the particular ranges for the lipid, protein, and sugar found in the matrix of the claimed particles. The contribution of Hanes to the art is the use of surfactants in particles for drug delivery to the pulmonary system and not the use of a particular combination of components (*e.g.*, 20-60% lipid, 10-30% protein, and 10-30% sugar) to form the matrix of the claimed microparticles.

Although Hanes may mention each of the materials recited in the claims, Hanes does not teach microparticles containing lipid, protein, and sugar. Instead, Hanes claims a microparticle comprising an agent and a surfactant, and separate, individual dependent claims allow for the incorporation of additional components, such as polymer or lipid. The claims of Hanes do not allow the incorporation of more than one component in addition to the agent and surfactant. The Examples in Hanes describe particles made with either: (1) poly[(p-carboxyphenoxy)-hexane anhydride], (2) poly(D,L-lactic-co-glycolic acid) (PLGA 50:50), (3) lysozyme, (4) dextran-DEAE, (5) trehalose, and (6) polyethylene glycol. The resulting particles only have *two* components in the matrix—lipid plus the other material.

Hanes does *not* describe the use of lipid, protein, and sugar in the matrix of the particles as claimed in the present invention. Since Hanes does not prepare any microparticles with any of the combinations of materials as claimed in the present invention, the specification of Hanes is not enabling for the microparticles of the present invention. In contrast, the present claimed invention (1) recites the use of a particular combination of three components selected from proteins, lipids, sugars, and synthetic polymers in the inventive microparticles, (2) produces such particles, and (3) demonstrates that such particles effectively deliver a physiologically-active agent which elicits the desired physiological response. Hanes describes the use of at most two components—a lipid; and a synthetic polymer, protein, or sugar. Since Hanes does not teach or even suggest a combination of three components in the recited ranges, Hanes cannot anticipate or render obvious the claimed invention. Applicant respectfully requests that the rejection be removed.

V. **Rejection under 35 U.S.C. § 103(a), as being unpatentable over Hanes *et al.*, U.S. Patent 5,855,913, taken with any of Grinstaff *et al.*, Sutton *et al.*, Rypacek *et al.*, and further in view of Wheeler *et al.*** Claims 1, 2, 7-24, 26, 27, 29-33, 37-40, 45-48, 51, 53, 54, 57-63, 65-69, and 73-79 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hanes *et al.* taken with any of Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.*, and further in view of Wheeler *et al.* The Examiner states that Hanes *et al.*, does not claim explicitly minor modification such as known DNAs, RNAs, or plasmids encoding for an antigen, ratios of agents being used in the formulations, and/or a particular combination of known matrix polymers (albumin and/or other known polymer), lipids and excipient(s) such as any other sugar (cellulose). The Examiner asserts that such modifications would have been obvious to one of ordinary skill in the art as minor modifications that can be practiced as a matter of design choice by a person of ordinary skill in the art, particularly in view of the totality of the prior art of record as set forth in Grinstaff *et al.*, Sutton *et al.*, or Rypacek *et al.* Applicant disagrees.

As discussed above, Hanes teaches microparticles that are greater than 5 μm in diameter (column 3, line 67-column 4, line 2), and teaches away from microparticles that are smaller than 5 μm (column 8, lines 8-12, 29-34). Given the teachings of Hanes, the results of the examples presented in the present application are surprising and unexpected. The lipid-protein-sugar particles that were described in the examples were all (1) smaller than 5 μm (page 35, Table 1, and page 52, Table 2), (2) stable within the animal, (3) able to effectively deliver the agent, and (4) able to elicit the desired pharmaceutical effect (pages 38-39, "*Effectiveness of sciatic nerve block*"). Hanes cannot render obvious the claimed microparticles that are smaller than 5 μm, regardless of the composition of the particles. Therefore, Applicant respectfully requests that the rejection be removed.

As discussed above, Grinstaff teaches microparticle comprising a cross-linked polymeric shell (column 6, lines 13-14 and column 8, lines 8-10, 34-53) and also teaches away from microparticles comprising a polymeric shell that is not cross-linked (column 20, lines 18-25). Similarly, Rypacek teaches a polymeric agent that is used to stabilize emulsions during the preparation of microparticles that are formed by means of cross-linking (page 1, lines 11-15). The microparticles of the present invention do not comprise a cross-linked polymeric shell or

emulsion ("Methods of Making Microparticles" page 25, line 9); therefore, Grinstaff and Rypacek do not teach the microparticles of the present invention, even when combined with the teachings of Hanes. If Hanes were combined with either Grinstaff, Rypacek, or both, they would teach microparticles larger than 5 μm in diameter in which the particles comprise a cross-linked polymeric matrix or emulsion. The combined references teach away from microparticles of the present invention, which are smaller than 5 μm in diameter, and do not comprise a cross-linked polymeric shell or emulsion. Therefore, Applicant respectfully requests that the rejection be removed.

Wheeler teaches lipid particles that are used to deliver nucleic acids and describes many difficulties associated with preparing particles for gene transfer, such as particle degradation (column 6, lines 33-40). Wheeler states that characteristics that make a particle an effective gene transfer vehicle generally make a carrier unstable in solution (column 2, lines 28-32). In order to overcome the difficulties of delivering nucleic acids using microparticles, Wheeler teaches lipid particles ranging from 50-150 nm in diameter (column 16, lines 35-36) that are used in the delivery of nucleic acids. The particles of the present invention are much larger, ranging from 0.5-5 μm, and are therefore not disclosed by Wheeler. In fact, Wheeler teaches away from using larger particles (column 16, lines 20-23).

Given that Wheeler teaches the many difficulties associated with making particles that are effective for gene transfer, it would not be obvious to alter the particles described by Wheeler by including additional particle components or increasing particle size. The inventive microparticles are not made obvious by Wheeler; therefore, the Applicant respectfully requests that the rejection be removed.

Even if all of these references were combined, they would not teach the present invention. For example, the combined references would teach microparticles of undetermined size, since Hanes teaches particles larger than 5 μm (and teaches away from smaller particles), and Wheeler teaches particles smaller than 0.15 μm (and teaches away from larger particles). Additionally, these microparticles would have been formed by cross-linking, since Grinstaff requires cross-linking (and teaches away from un-cross-linked particles) and Rypacek provides a stabilizing agent to be used in emulsions prior to cross-linking. Furthermore, these

microparticles would have an undetermined physical description, since Sutton teaches hollow microparticles, and Grinstaff teaches microparticles that encapsulate an agent (please see discussion above). Therefore, these references combined would not render obvious the inventive particles. Inventive particles have a *defined* size (which is smaller than the microparticles described by Hanes, but larger than the microparticles described by Wheeler), are *not cross-linked* (which is in contrast to the teachings of Grinstaff and Rypacek), and are *not hollow* (which is in contrast to the teachings of Sutton).

Furthermore, as described above, Hanes does not teach microparticles comprising three components. In response to the Applicant's argument in the last Response that Hanes does not teach or suggest the particular combinations of materials recited in the claim, the Examiner states that "there clearly exists general art accepted motivations for formulating an excipient such as a sugar into the DPPC/protein/polymer blends of Hanes." However, Hanes does not teach a DPPC/protein/polymer blend. Hanes at most teaches two components in the matrix of the particles—a lipid and another material. Plus, there is no motivation from any of the references to include sugar in the particles of Hanes. Applicant respectfully submits that the Examiner has failed to adequately identify a suggestion or motivation to combine the references. The Examiner has not pointed to any statement in any of the references that would provide a suggestion or motivation to combine them. Instead, the Examiner's suggestion that modifications (such as DNAs, RNAs, or plasmids encoding for an antigen; ratios of agents being used in the formulations; and/or a particular combination of known matrix polymers, lipids and excipients) would have been obvious to one of ordinary skill in the art, and is thus based on hindsight. This is not allowed.

Applicant submits that the Examiner has not met his burden of showing a suggestion, teaching, or motivation to combine prior teachings that is "clear and particular" as required by the Federal Circuit and has failed to heed the Federal Circuit's admonition that:

> "The best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching,

> or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight."

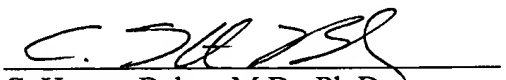
In re Dembiczak, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999). In light of the court's opinion, the Examiner fails to establish a *prima facie* case of obviousness. The Examiner has not pointed to any statement in any of the references that would provide a suggestion or motivation to combine them. Therefore, the combination of references does not render obvious the claimed invention, and Applicant respectfully requests that the rejection be removed.

In view of the forgoing amendments and arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

The Applicant thanks the Examiner for fully considering this response and requests a phone discussion with the Examiner before issuance of the Final Office Action, at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5215 (direct dial).

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,



C. Hunter Baker, M.D., Ph.D.
Registration Number: 46,533

Choate, Hall & Stewart
Two International Place
Boston, MA 02110
(617) 248-5215
Date: August 24, 2006